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## Advanced therapy medicinal products in surgery

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**Advanced therapy medicinal products in surgery**

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3 **Advanced therapy medicinal products in surgery**  
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17 Short Report  
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Complex gene, cell or tissue-based solutions are increasingly being used to treat diseases, which have direct relevance to surgery in that they provide alternatives to surgery or require surgical intervention for their delivery. New products are being developed in almost every branch of surgery to correct gene defects, assist tissue repair or regeneration, to treat cancer or to replace damaged tissues or organs. Such products are grouped under the umbrella term advanced therapy medicinal products (ATMP)<sup>1</sup>. There are three main product areas considered as ATMPs (Figure 1). Gene therapy based medicines typically involve the delivery of strands of recombinant DNA designed to correct a gene defect. Novel somatic gene editing technologies including clustered regularly interspaced short palindromic repeats–CRISPR-associated proteins (CRISPR-Cas), may also fall under the same classification and regulatory framework as recombinant DNA treatments although the scientific approach and mechanism of action is different<sup>2</sup>.

The second, ATMP type is somatic cell therapy medicine products (sCTMP)<sup>3</sup>. This describes a therapy based around cells or tissues, which have undergone substantial manipulation so that biological properties, physiology or structural properties have been altered. Also included are products involving cells or tissues where the intention is that they will not be used for the same functions in the recipient as they were in the donor. In both cases the products are intended to be administered to humans for the purpose of treating, preventing or diagnosing disease through the action of its cells. Many stem cell therapies and chimaeric antigen receptor T cell (CAR Tcell) therapies fall within this category sCTMP.

The third type of ATMP is tissue-engineered medicinal products. This covers products such as decellularised scaffolds and also products where cells are combined with a matrix or scaffold. In the case of both somatic cell therapy medicine products and tissue engineered medicines cells are often derived from the patient and modified before being given back in an immunologically autologous fashion. Tissue engineered products may use allogeneic material or animal tissue which has been treated to remove HLA antigens for example skin, bone or cartilage scaffolds.

All ATMPs should be supported by robust research evidence base which depending on the specific ATMP in question may require large animal studies. Unfortunately some of the early developments in ATMPs did not comply with existent research governance and regulatory steps and have caused harm to patients. Notable cases of patient harm have arisen through attempts at tracheal transplantation leading to fatalities<sup>4,5</sup> and unregulated ocular injection of stem cells leading to blindness<sup>6</sup>. It is critically important that surgeons involved in this space fully understand their roles and responsibilities within the regulatory frameworks designed for the safe administration of ATMPs and that patients are properly protected.

Responsibility for regulation of ATMPs falls under the European Medicines Agency (EMA) in Europe and under the Food and Drug Administration in USA. In the United Kingdom regulation is also subject to the Medicines

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3 Healthcare Regulatory Authority MHRA<sup>7</sup> and will be subject to equivalent  
4 national regulation in other European countries. There are multiple areas  
5 where surgeons may be involved in the development pathway of ATMPs  
6 (Figure 2). In the United Kingdom the acquisition of cells or tissues from a  
7 donor, whether this is for an autologous or allogeneic ATMP must be  
8 conducted under the Human Tissue Act<sup>8,9</sup> and with written informed consent  
9 of the donor or in the case of a deceased donor with family assent. Such  
10 consent or assent should include details of the intended use of the cells or  
11 tissues and their final destination. If cells or tissues are being removed for  
12 commercial development of an ATMP then this should also be made clear to  
13 the donor. Responsibility for taking consent and ensuring that appropriate  
14 HTA approvals are in place may sit with the surgeon undertaking the  
15 procedure. Collection of cells or tissues should be performed following a  
16 standard operating procedure which maintains adopts aseptic practice,  
17 maintains sterility through transfer or storage and which seeks to optimize the  
18 condition of material removed for ATMP production. The handling of cells or  
19 tissues removed in the operating theatre are also likely to involve the surgeon  
20 who should be fluent with the appropriate protocols. Cells or tissues may  
21 require storage or transfer and this should also be covered by a standard  
22 operating procedure to ensure a safe chain of custody of the material to the  
23 laboratory or local storage and under optimal conditions as required.  
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28 Manipulation of cells or tissues in the United Kingdom must be undertaken in  
29 a Good Manufacturing Process compliant laboratory, which has been  
30 designated for this purpose. This is to ensure that ATMP are manufactured to  
31 the best possible standards under a regulatory framework and specifically  
32 avoiding risks such as cross contamination of cells or microbiological  
33 contamination, which could have potentially devastating consequences for the  
34 recipient. Some tissue engineered products may be manufactured using a  
35 scaffold which is specific to the recipient and which requires the involvement  
36 of a surgeon in design of a scaffold for example facial reconstructive surgery.  
37 Once the manufacture of an ATMP has been completed and has completed  
38 quality assurance checks it is issued to the clinical area. Consent of the  
39 recipient must be fully informed and should discuss alternative treatments as  
40 well as the option of no intervention. Known and theoretical risks should be  
41 discussed with recipients and this again may fall within the responsibility of  
42 the surgeon. Administration of the ATMP should follow a standard operating  
43 procedure, which maintains asepsis and optimizes the conditions for delivery  
44 of the ATMP. Equally any supporting staff involved in the administration or  
45 surgical delivery of an ATMP must be fully aware of the SOP and conditions  
46 for it's administration. The manufacture and administration of many ATMPs is  
47 complex and involves scientists, pharmacists, regulators, clinical  
48 administration and other clinicians in addition to surgeons. Finally the surgeon  
49 has a responsibility to follow up patients treated with an ATMP and to report  
50 and manage any adverse events which might be related to the ATMP or  
51 surgery required for it's administration.  
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57 The development of novel ATMPs whether they be gene therapy or stem cell  
58 or other cell therapy products either alone or in combination with scaffold,  
59 matrices or other materials represent an exciting and innovative area of  
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3 science. This new branch of medicine is expanding rapidly and has the  
4 potential to offer hope to patients in a number of difficult-to-treat diseases.  
5 Surgeons will be expected to play significant roles in the acquisition of cells  
6 and tissues for ATMP manufacture, assisting in ATMP design in certain  
7 circumstances and probably most frequently in the delivery or administration  
8 of ATMPs to patients. It is critical that the surgical community is aware of the  
9 regulatory framework, which exists to maintain the quality and safety of ATMP  
10 and to protect patients from harm. Similarly it is important that surgeons fully  
11 understand their role, how this will interact with others in the ATMP  
12 manufacturing and delivery pathway and their responsibilities to patients.  
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## 17 References

- 18  
19 1. [https://www.ema.europa.eu/en/human-regulatory/overview/advanced-](https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#stem-cells-section)  
20 [therapy-medicinal-products-overview#stem-cells-section](https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#stem-cells-section) accessed  
21 07/07/2022
- 22  
23 2. Rigter, T., Klein, D., Weinreich, S.S. *et al.* Moving somatic gene editing  
24 to the clinic: routes to market access and reimbursement in  
25 Europe. *Eur J Hum Genet* 29, 1477–1484 (2021).
- 26  
27 3. [https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-](https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-Somatic-Cell-Therapy-Products-V1-July-2020.pdf)  
28 [Institutional-Readiness-for-Somatic-Cell-Therapy-Products-V1-July-](https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-Somatic-Cell-Therapy-Products-V1-July-2020.pdf)  
29 [2020.pdf](https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-Somatic-Cell-Therapy-Products-V1-July-2020.pdf) accessed 07/07/2022.
- 30  
31 4. Disgraced tracheal transplant surgeon is handed 16 month prison  
32 sentence in Italy. *BMJ* 2019;367:l6676.
- 33  
34 5. [https://www.theguardian.com/world/2022/jun/16/sweden-surgeon-](https://www.theguardian.com/world/2022/jun/16/sweden-surgeon-convicted-of-bodily-harm-over-synthetic-trachea-transplants)  
35 [convicted-of-bodily-harm-over-synthetic-trachea-transplants](https://www.theguardian.com/world/2022/jun/16/sweden-surgeon-convicted-of-bodily-harm-over-synthetic-trachea-transplants) accessed  
36 07/07/2022.
- 37  
38 6. [https://www.livescience.com/58287-unproven-stem-cell-therapy-](https://www.livescience.com/58287-unproven-stem-cell-therapy-blindness.html)  
39 [blindness.html](https://www.livescience.com/58287-unproven-stem-cell-therapy-blindness.html) accessed 07/07/2022.
- 40  
41 7. [https://www.gov.uk/guidance/advanced-therapy-medicinal-products-](https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing)  
42 [regulation-and-licensing](https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing) accessed 07/07/2022.
- 43  
44 8. Living donor organ or tissue donation  
45 [https://content.hta.gov.uk/sites/default/files/2020-](https://content.hta.gov.uk/sites/default/files/2020-11/Code%20F%20part%201.pdf)  
46 [11/Code%20F%20part%201.pdf](https://content.hta.gov.uk/sites/default/files/2020-11/Code%20F%20part%201.pdf) accessed 07/07/2022.
- 47  
48 9. Deceased donor organ and tissue donation  
49 [https://content.hta.gov.uk/sites/default/files/2020-](https://content.hta.gov.uk/sites/default/files/2020-11/Code%20F%20part%202.pdf)  
50 [11/Code%20F%20part%202.pdf](https://content.hta.gov.uk/sites/default/files/2020-11/Code%20F%20part%202.pdf) accessed 07/07/2022.
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3 Figure Legends  
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5 Figure 1.  
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8 Classification of advanced therapy medicinal products ATMPs with examples and  
9 example applications  
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13 Figure 2.  
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16 Manufacturing pathway of advanced therapy medicinal products ATMPs. Blue  
17 boxes indicate where surgeons are most likely to be directly involved in the  
18 pathway  
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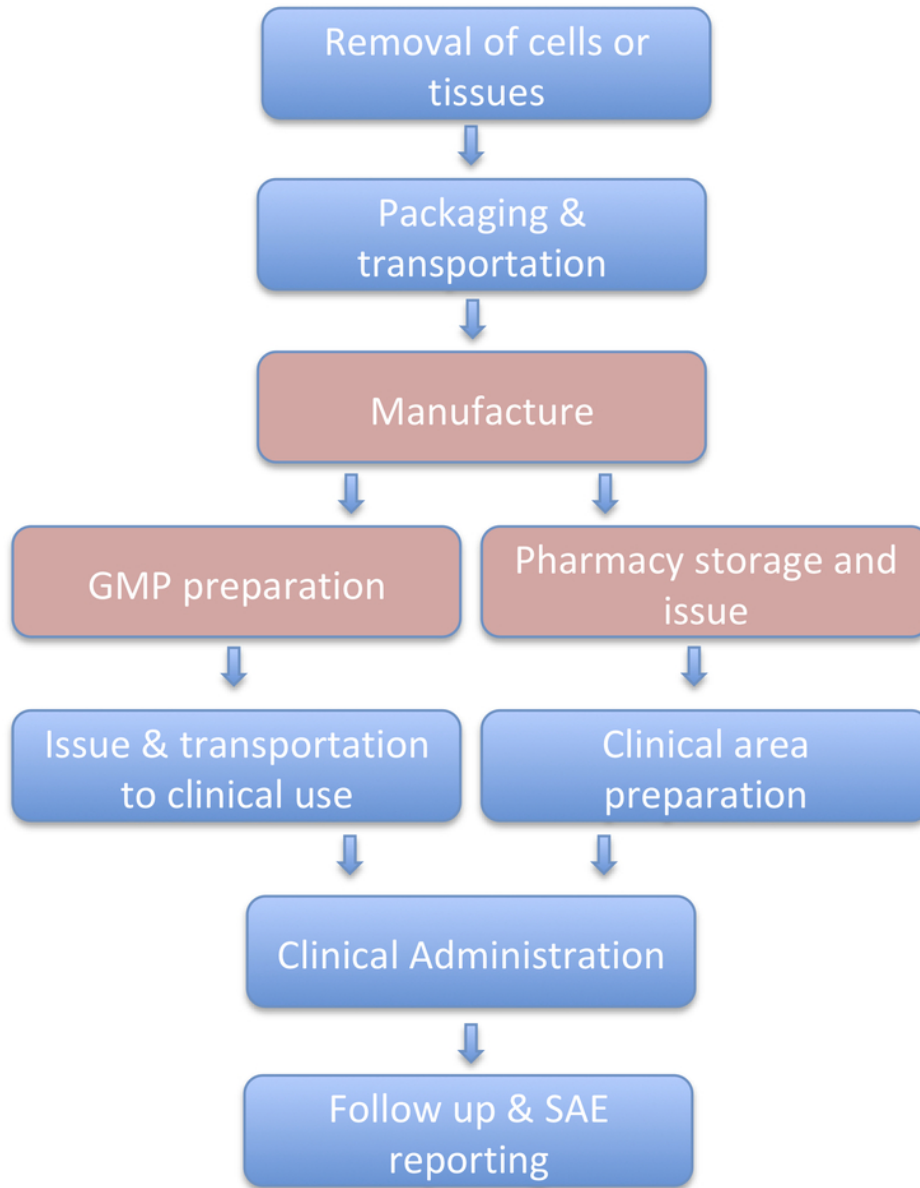


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Advanced therapy medicinal products	Example	Example application
 Gene therapy	Genetic modification of gene associated with disease	 Correction of single gene defect retinal disease
 Somatic cell therapy	Human mesenchymal cells used to promote healing	 Cartilage repair
 Tissue engineered medicines	Decellularised scaffold or Scaffold containing autologous or allogeneic modified cells	 Skin repair burns  Diabetic ulcer healing

Classification of advanced therapy medicinal products ATMPs with examples and example applications

237x126mm (150 x 150 DPI)



Manufacturing pathway of advanced therapy medicinal products ATMPs. Blue boxes indicate where surgeons are most likely to be directly involved in the pathway

124x159mm (150 x 150 DPI)